

WHAT IS CLAIMED IS:

1. A method of inducing differentiation of a non-cardiomyocyte into a cardiomyocyte, said method comprising stimulating oxytocin receptor (OTR) activity in said non-cardiomyocyte.
2. The method of claim 1, wherein said method comprises contacting said non-cardiomyocyte with an agent capable of stimulating OTR activity.
3. The method of claim 2, wherein said agent is selected from the group consisting of oxytocin or a functional derivative thereof, retinoic acid and triiodothyronine (T₃).
4. The method of claim 3, wherein said oxytocin or functional derivative thereof has the structure:
- 20
- The diagram shows a peptide chain: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-CO-R. A horizontal line connects the sulfur atom (S) of the first Cys residue to the sulfur atom (S) of the fourth Cys residue, with a vertical line extending upwards from the first Cys and another vertical line extending downwards from the fourth Cys, indicating a disulfide bridge.
- Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-CO-R
- wherein R is selected from the group consisting of OH, NH₂, Gly, Gly-Lys and Gly-Lys-Arg.
5. The method of claim 1, wherein the method comprises introducing into the non-cardiomyocyte a nucleic acid capable of encoding oxytocin or an oxytocin-related compound.
6. The method of claim 5, wherein the nucleic acid is selected from the group consisting of:
- (a) SEQ ID NO:5;
- (b) a nucleic acid sequence capable of

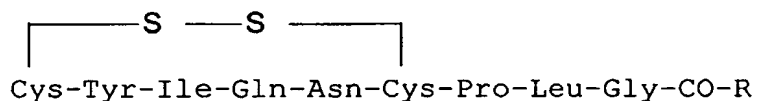
encoding SEQ ID NO:6; and

- (c) a nucleic acid sequence substantially identical to (a) or (b).

- 5 7. The method of claim 1, wherein said non-cardiomyocyte is a stem or progenitor cell.
8. The method of claim 7, wherein said stem or progenitor cell is selected from the group consisting of embryonic
10 and adult stem or progenitor cells.
9. The method of claim 7, wherein said stem or progenitor cell is selected from the group consisting of circulating and non-circulating stem or progenitor cells.
- 15 10. The method of claim 7, wherein said method is performed *in vitro*.
11. The method of claim 7, wherein said method is performed
20 *in vivo*.
12. The method of claim 1, wherein said cardiomyocyte is characterized by an alteration of a phenotypic feature relative to said non-cardiomyocyte, wherein said
25 phenotypic feature is selected from the group consisting of:
 - (a) level of oxytocin receptor (OTR) protein or OTR-encoding nucleic acid;
 - (b) level of ANP protein or ANP-encoding nucleic acid;
 - 30 (c) level of muscular MHC protein or muscular MHC-encoding nucleic acid;
 - (d) level of DHPR-alpha1 protein or DHPR-alpha1-encoding nucleic acid;
 - (e) level of sarcomeric marker proteins;
 - 35 (f) level of ion channels;

- (g) mitochondrial dye retention;
- (h) appearance of rhythmic beats; and
- (i) chronotropic responses.

- 5 13. A method of treating a disease characterized by
cardiomyocyte loss or deficiency in an animal, said
method comprising stimulating oxytocin receptor (OTR)
activity in a non-cardiomyocyte cell of said animal.
- 10 14. The method of claim 13, wherein said method comprises
administering an agent capable of stimulating OTR
activity to said animal.
- 15 15. The method of claim 14, wherein said agent is selected
from the group consisting of oxytocin or a functional
derivative thereof, retinoic acid and triiodothyronine
(T₃).
- 20 16. The method of claim 15, wherein said oxytocin or
functional derivative thereof has the structure:



- 25 wherein R is selected from the group consisting of OH, NH₂,
Gly, Gly-Lys and Gly-Lys-Arg.
- 30 17. The method of claim 15, wherein the method comprises
administering a nucleic acid capable of encoding oxytocin
or a functional derivative thereof to said animal.
18. The method of claim 17, wherein the nucleic acid is
selected from the group consisting of:
- (a) SEQ ID NO:5;
 - (b) a nucleic acid sequence capable of
- 35

encoding SEQ ID NO:6; and

(c) a nucleic acid sequence substantially identical to (a) or (b).

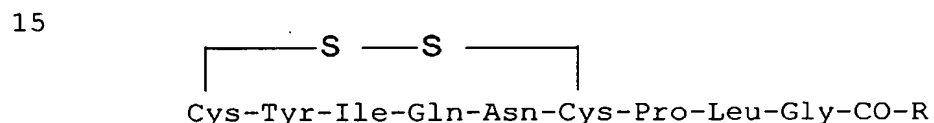
- 5 19. The method of claim 13, wherein said non-cardiomyocyte is a stem or progenitor cell.
20. The method of claim 19, wherein said stem or progenitor cell is selected from the group consisting of circulating
10 and non-circulating stem or progenitor cells.
21. The method of claim 13, wherein said animal is a mammal.
22. The method of claim 13, wherein said animal is a human.
15
23. The method of claim 13, wherein said disease is selected from the group consisting of cardiac congenital dysfunctions, aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial
20 ischemia.
24. A method of treating a disease characterized by cardiomyocyte loss or deficiency in an animal, said method comprising:
- 25 (a) inducing, using the method of claim 1, differentiation of a non-cardiomyocyte cell into a cardiomyocyte; and
- (b) implanting said cardiomyocyte into said animal.
- 30 25. The method of claim 24, wherein said animal is a mammal.
26. The method of claim 24, wherein said animal is a human.
27. The method of claim 24 where said disease is selected from
35 the group consisting of cardiac congenital dysfunctions,

aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial ischemia.

28. The method of claim 24, wherein said method comprises
5 contacting said non-cardiomyocyte with an agent capable of stimulating OTR activity.

29. The method of claim 28, wherein said agent is selected
10 from the group consisting of oxytocin or a functional derivative thereof, retinoic acid and triiodothyronine (T₃).

30. The method of claim 29, wherein said oxytocin or functional derivative thereof has the structure:



wherein R is selected from the group consisting of OH, NH₂,
20 Gly, Gly-Lys and Gly-Lys-Arg.

31. The method of claim 24, wherein the method comprises
25 introducing into the non-cardiomyocyte a nucleic acid capable of encoding oxytocin or a functional derivative thereof.

32. The method of claim 31, wherein the nucleic acid is selected from the group consisting of:

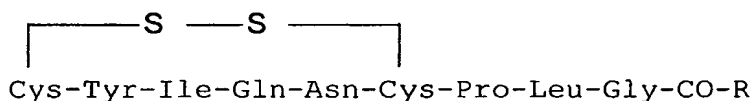
- (a) SEQ ID NO:5;
30 (b) a nucleic acid sequence capable of encoding SEQ ID NO:6; and
(c) a nucleic acid sequence substantially identical to (a) or (b).

33. The method of claim 24, wherein said non-cardiomyocyte is a stem or progenitor cell.
34. The method of claim 33, wherein said stem or progenitor cell is selected from the group consisting of embryonic and adult stem or progenitor cells.
35. The method of claim 33, wherein said stem or progenitor cell is selected from the group consisting of circulating and non-circulating stem or progenitor cells.
36. The method of claim 24, wherein said non-cardiomyocyte is autologous to said animal.
37. The method of claim 36, said method further comprising obtaining said non-cardiomyocyte from said animal prior to inducing said differentiation.
38. The method of claim 24, wherein said non-cardiomyocyte is non-autologous to said animal.
39. The method of claim 38, wherein said non-cardiomyocyte is allogenic to said animal.
40. The method of claim 38, wherein said non-cardiomyocyte is xenogenic to said animal.
41. The method of claim 24, wherein said cardiomyocyte is characterized by an alteration of a phenotypic feature relative to said non-cardiomyocyte, wherein said phenotypic feature is selected from the group consisting of:
- (a) level of oxytocin receptor (OTR) protein or OTR-encoding nucleic acid;
 - (b) level of ANP protein or ANP-encoding nucleic acid;

- (c) level of muscular MHC protein or muscular MHC-encoding nucleic acid;
- (d) level of DHPR-alpha1 protein or DHPR-alpha1-encoding nucleic acid;
- 5 (e) level of sarcomeric marker proteins;
- (f) level of ion channels;
- (g) mitochondrial dye retention;
- (h) appearance of rhythmic beats; and
- (i) chronotropic responses.
- 10 42. Use of an agent capable of stimulating OTR activity for treating a disease characterized by cardiomyocyte loss or deficiency in an animal.
- 15 43. The use of claim 42, wherein said agent is selected from the group consisting of oxytocin or a functional derivative thereof, retinoic acid and triiodothyronine (T₃).
- 20 44. The use of claim 43, wherein said oxytocin or functional derivative thereof has the structure:
- $$\begin{array}{c} \boxed{\text{S} \text{ --- } \text{S}} \\ \text{Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-CO-R} \end{array}$$
- 25 wherein R is selected from the group consisting of OH, NH₂, Gly, Gly-Lys and Gly-Lys-Arg.
45. The use of claim 42, wherein said animal is a mammal.
- 30 46. The use of claim 42, wherein said animal is a human.
47. The use of claim 42, where said disease is selected from the group consisting of cardiac congenital dysfunctions,

aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial ischemia.

48. A commercial package comprising an agent capable of stimulating OTR activity together with instructions for treating a disease characterized by cardiomyocyte loss or deficiency in an animal.
49. The commercial package of claim 48, wherein said agent is selected from the group consisting of oxytocin or a functional derivative thereof, retinoic acid and triiodothyronine (T₃).
50. The commercial package of claim 49, wherein said oxytocin or functional derivative thereof has the structure:

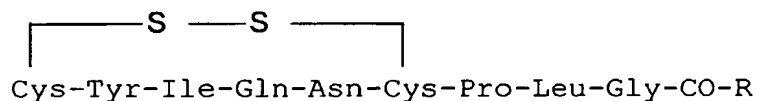


- wherein R is selected from the group consisting of OH, NH₂, Gly, Gly-Lys and Gly-Lys-Arg.
51. The commercial package of claim 48, wherein said animal is a mammal.
52. The commercial package of claim 48, wherein said animal is a human.
53. The commercial package of claim 48, where said disease is selected from the group consisting of cardiac congenital dysfunctions, aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial ischemia.

54. A commercial package comprising an agent capable of stimulating OTR activity together with instructions for inducing differentiation of a non-cardiomyocyte to a cardiomyocyte.

55. The commercial package of claim 54, wherein said agent is selected from the group consisting of oxytocin or a functional derivative thereof, retinoic acid and triiodothyronine (T₃).

56. The commercial package of claim 55, wherein said oxytocin or functional derivative thereof has the structure:



wherein R is selected from the group consisting of OH, NH₂, Gly, Gly-Lys and Gly-Lys-Arg.

57. A commercial package comprising a culture medium comprising oxytocin or a functional derivative thereof; together with instructions for culturing a non-cardiomyocyte in said culture medium thereby to induce differentiation of said non-cardiomyocyte into a cardiomyocyte.

58. The commercial package of claim 57, wherein said non-cardiomyocyte is a mammalian non-cardiomyocyte.

59. The commercial package of claim 57, wherein said non-cardiomyocyte is a human non-cardiomyocyte.

60. The commercial package of claim 57, wherein said non-cardiomyocyte is a stem or progenitor cell.

61. The commercial package of claim 57, wherein said oxytocin or functional derivative thereof is present in said medium at a concentration from about 10^{-10} M to about 10^{-4} M.

5

62. The commercial package of claim 61, wherein said oxytocin or functional derivative thereof is present in said medium at a concentration from about 10^{-9} M to about 10^{-6} M.

10

63. The commercial package of claim 62, wherein said oxytocin or a functional derivative thereof is present in said medium at a concentration from about 10^{-8} M to about 10^{-7} M.

15

64. A composition for treatment of a disease characterized by cardiomyocyte loss or deficiency comprising oxytocin or a functional derivative thereof in and a pharmaceutically acceptable carrier.

20

65. The composition of claim 64, wherein said disease is selected from the group consisting of cardiac congenital dysfunctions, aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial ischemia.

25

66. A method of identifying or characterizing a compound for inducing differentiation of a non-cardiomyocyte cell into a cardiomyocyte, said method comprising:

30

(d) contacting a test compound with a cell comprising an oxytocin receptor (OTR) or an OTR-encoding nucleic acid; and

(e) determining whether OTR activity or expression is increased in the presence of the test compound, said increase in OTR activity or expression being an

35

indication that the test compound may be used for inducing differentiation of a non-cardiomyocyte into a cardiomyocyte.

- 5 67. A method of identifying or characterizing a compound for treatment of a disease characterized by cardiomyocyte loss or deficiency, said method comprising:
- 10 (a) contacting a test compound with a cell comprising an oxytocin receptor (OTR) or an OTR-encoding nucleic acid; and
- (b) determining whether OTR activity or expression is increased in the presence of the test compound, said increase in OTR activity or expression being an indication that the test compound may be used for
- 15 for treatment of a disease characterized by cardiomyocyte loss or deficiency.
68. The method of claim 67, wherein said disease is selected from the group consisting of cardiac congenital
- 20 dysfunctions, aging-related heart pathologies, heart infarction, congestive heart failure and acute myocardial ischemia.
69. A method of identifying a cell capable of differentiation
- 25 to a cardiomyocyte, said method comprising determining whether OTR activity or expression is present in said cell, said presence being an indication that said cell is capable of differentiation to a cardiomyocyte.